Specifications During Early Development
- FDA Perspectives -

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Overview

• Kirby Wong-Moon has summarized the proposals in the IQ Consortium paper on specifications in early development

• I will highlight some areas for discussion, where a CMC regulator may have questions

• Based on my personal experience and discussion with colleagues in CDER
  – There is no current guidance development work at CDER on specs in early development
Outline

• Common goals for Early Development
• How things look from the reviewers' perspectives
• Questions and discussion topics related to IQ Consortium proposals
  – Drug Substance (DS)
  – Drug Product (DP)
Mutual Goals in Early Development

Objectives

• Insure safety of patient
• Get drugs through First in Human and early studies efficiently to identify promising candidates
• Collect information to determine which attributes of DS and DP are important for safety and efficacy

Review Perspectives

• Appropriate specs with reasonable flexibility can help meet these goals
• Specs and other parts of submission need to be clear to reviewer to help avoid unnecessary questions or delays
Specifications in Early Development

• General concept that specifications evolve over development is well accepted
• “The regulations at 312.23(a)(7)(i) emphasize the graded nature of manufacturing and controls information.”
  • Content and Format of INDs for Phase 1 Studies (FDA 1995)
• Can more specifics be agreed upon?
Perceptions of Risk

• Variety of Products and Clinical Indications; Individual review experience
  – Result: CDER’s risk assessments will vary from drug to drug
  – Value in applicant providing own risk-assessment?

Possible Discussion Point: pros/cons of including risk-assessment as part of the justification for specifications?
Feedback on IQ Consortium Paper

- Terminology -

• “Report Results” and “For Information Only”
• “Internal Tests”
• “In-Process Controls”
• These are parts of the Control Strategy
Terminology – “Report Results”

• Listing a test on the spec with AC=“Report Results” provides clarity that this attribute is being studied to see if it is a CQA.
  – Commonly seen in early development for attributes like particle size or solid-state form of DS
  – In some cases could lead to questions for safety-related attributes like impurities

Possible Discussion Point: Do “Report Results” and “For Information Only” in IQ Consortium paper have different meanings?
Terminology – “Internal Tests”

“Internal Tests” could mean:

1. Internal Action Limit for test with “report limits”
2. Internal Action Limit to assure meeting regulatory AC over shelf life
3. Collect information, but attribute not listed on spec
   • will reviewer know this is being done?

Possible Discussion Point: pros/cons of this third type of Internal Control
Terminology – “In-Process Controls”

Example of “In-Process Control” from IQ Consortium paper:

– Powder-in-bottle: “weight check may be omitted from the DP specifications if it is conducted as part of an in-process control.”

– How are IPCs communicated to the reviewer?
  • Would this IPC be listed in manufacturing process section?

Possible Discussion Point: could summarizing the control strategy help provide clarity to reviewer?
Feedback on IQ Consortium Paper
- Impurity Specifications -

• Focus on Drug Substance
  – General Qualification
  – Identification Threshold
  – Qualification Threshold
  – Residual Solvents
  – Mutagenic Impurities
Control of Impurities in Early Development

Overall Discussion

• IQ Consortium paper: “If the tox batch is also intended to be used in a clinical study, there is an advantage in that the qualification of impurities for the clinical studies is inherently assured.”

Possible Discussion Point: Pros and cons of Clinical batch = Tox batch
Identification Threshold for Phase 1 and 2a

• IQ Consortium paper proposes a 3-fold higher ID threshold compared to ICH Q3A
• Seems generally consistent with FDA current guidance and practice:
  – “Procedures to evaluate impurities to support an NDA (e.g., recommended identification levels) may not be practical at this point in drug development. Suitable limits should be established based on manufacturing experience, stability data, and safety considerations.”
• INDs for Phase 2 and Phase 3 Studies – CMC Info (FDA 2003)
Identification Threshold

• IQ Consortium paper:
  – “An identification (ID) threshold of three times the ICH Q3A limit (0.3%) is proposed for unknown impurities that have not been qualified by toxicology studies”
  – “ID threshold can be set higher for unknown impurities that have already been qualified”

Possible Discussion Point: Is this intended to prioritize the identification of impurities that are not qualified by the early tox studies?
A more difficult topic: Qualification Thresholds

- Multidisciplinary Topic
  - Preclinical Safety (Pharmacology/Toxicology)
  - CMC
Qualification Thresholds

• The maximum level of a specific impurity that is qualified by safety studies is not always clear to the CMC reviewer
• Often the level in the proposed clinical lot is ≤ level in the tox lot(s)
• Higher levels may still be qualified, based on higher doses in animal safety studies
  – CMC reviewer relies on Pharm/Tox input
  – Or, we rely on clear statement by Applicant, (E.g., “The level of impurities are assessed throughout development to ensure that they will always be held at or below levels qualified in safety studies.”)
Qualification Thresholds

• Multidisciplinary topic – proposals must be considered from Preclinical Safety perspective as well as CMC

• Depending on the individual drug, indication, etc, the following approaches may help in early development (Phase 1 and 2a):
  – Match impurity profiles of clinical and tox batches
  – Justify cases where impurities are not qualified by tox studies
  – Ensure future tox studies are conducted with material that closely matches the clinical material
Qualification Thresholds

• ICH Q3A:
  – “The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified.”
  – A higher level “can also be justified based on an analysis of the actual amount of impurity administered in previous relevant safety studies.”
Qualification Thresholds

• IQ Consortium paper: “For individual impurities that exceed the 0.5% threshold but are supported by toxicology data, an upper limit of not more than (NMT) 1.0% in the DS is appropriate for this stage of development.”

Possible Discussion Point: Does this mean that the impurity was qualified at ≥ 1.0% by safety studies?
Residual Solvents

• IQ Consortium paper: “The early development specifications for residual-solvent control are often set using the ICH established limits, including the consideration of maximum daily dose for Class 2 solvents (Option 2).”

• Q3C: (at NDA stage): Option 2 limits are considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum.

• From FDA perspective, relatively high levels for Option 2 could lead to this question: Will the DS CQAs or DP performance be altered?
Mutagenic Impurities

- ICH M7 Published for Public Comment 2Q2013
- M7 has parallel concepts to some of the IQ Consortium proposals
- ICH M7:
  - It is recognized that product and process knowledge increases over the course of development and therefore it is expected that data to support control strategies in the clinical development trial phases will be less than at the marketing registration phase.
  - A risk-based approach based on process chemistry fundamentals is encouraged to prioritize analytical efforts on those impurities with the highest likelihood of being present in the drug substance or drug product.
  - It is expected that the number of structures assessed for mutagenicity, and the collection of analytical data will both increase throughout the clinical development period.
  - For products in clinical development, the thresholds outlined in ICHQ3A/B do not apply and it is acknowledged that the thresholds for actual impurities and degradants will typically be higher than those outlined in ICHQ3A/B.
Feedback on IQ Consortium Paper
- Drug Product Topics -

• Water Content
• In Vitro Release Specifications
  – “PIB”: Powder (DS) in Bottle
  – “PIC”: Powder (DS) in Capsule
• Nomenclature of Salts
Water content in Drug Product

- “Report Results” at early stages is fairly common in FDA experience

Possible Discussion Points:
- Value to use open-dish studies to understand impact on DP quality attributes?
- Pros/cons of tightening in later stages based on manufacturing capability?
In Vitro Release: DS-in-Bottle

• IQ Consortium paper (Table III): “No In Vitro release test for DS-in-Bottle.”

• FDA perspectives:
  – When DS undergoes almost instantaneous dissolution in the chosen vehicle upon shaking (within few seconds) at room temperature, no investigation or recording of dissolution time is necessary in early development (Phase 1 and 2a).
  – When DS forms a suspension after reconstitution, we recommend at least “report” dissolution results in the specification.
In Vitro Release: DS-in-Capsule

• IQ Consortium paper: “…disintegration test per USP General Chapter <701> is recommended to ensure that the capsules rupture to allow the release of the drug for absorption.”

• FDA perspectives:
  – Disintegration / Rupture testing within 15 min is generally sufficient for highly-soluble DS (Class I DS by BCS classification) in early development (Phase 1 and 2a).
    • This is also generally appropriate for capsules with highly-soluble DS formulated with excipients in Phase 1 and 2a
  – For the other classes of drugs, solubility and/or permeability are the limiting steps to absorption. Dissolution testing of these drugs is critical. Therefore, we recommend at least “report” dissolution results in the specification.
Additional Point to Consider for Dissolution in Early Development

FDA perspectives:

• Early knowledge of dissolution behavior will aid final formulation development to resolve problems associated with efficacy (less dissolves compared to early clinical formulation) or safety (more dissolves).

• Sponsors are encouraged to pursue rational and appropriate choices for dissolution methodology (e.g., media, apparatus, analysis, and specifications) early on that may provide for the acquisition of more product knowledge from the beginning (via higher quality data) without adding undue burden.
  – For example, the minimal use of surfactant and not over agitating the media to achieve dissolution under conditions which may better reflect adequate discrimination for future quality control and / or clinical relevance as development proceeds.
Naming of Salts
- Relevant to Early Development -

• CDER Mapp 5021.1 published Feb 2013
• Default strategy: strength of the DP should be based on the active moiety (free acid or base); name will also match
• Exception within the Policy if salt form has clinically relevant effect on absorption, distribution, metabolism, or excretion, etc.
• If considering this exception, discuss with FDA before implementing
Conclusions

Breakout Discussions offer opportunities to:

- Send observations and suggestions from your perspective back to FDA
- Exchange ideas on best practices with other pharmaceutical scientists
- Share ideas on using risk/benefit approaches to optimize Phase 1 and 2a studies
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